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Histologic Correlates of Angiographic Chronic Total Coronary Artery Occlusions

Influence of Occlusion Duration on Neovascular Channel Patterns and Intimal Plaque Composition

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Objectives. **Age-related changes in histologic composition and neovascular channel (NC) pattern of angiographic chronic total coronary artery occlusions (CTOs) were studied to define histologic correlates of age-related revascularization profiles and neovascular channel formation.**

Background. **Revascularization of CTOs is frequently characterized by inability to cross or dilate the lesion and a high incidence of reocclusion or restenosis but low periprocedural ischemic complication rates. Little is known about the histopathologic basis of these observations.**

Methods. **Ninety-six angiographic CTOs from autopsy studies in 61 patients who had undergone coronary angiography within 3 months of death were studied. Abrupt plaque rupture was excluded. Occlusion segments were analyzed for 1) histologic composition as a function of lesion age; and 2) NC pattern as a function of lesion age and intimal plaque (IP) composition.**

Results. **Cholesterol and foam cell–laden IP was more frequent in younger lesions ($p = 0.0007$), whereas fibrocalcific IP increased with CTO age ($p = 0.008$). IP NCs arose directly from adventitial vasa vasorum and were anatomically and quantitatively related in terms of number and size ($p = 0.0001$) to the extent of IP cellular inflammation. IP cellular inflammation exceeded that found in the adventitia ($p < 0.001$) or media ($p = 0.0001$) across all CTO ages. In CTOs <1 year old, the adventitia was associated with a larger number and size of NCs relative to the IP ($p = 0.0006$ and $p = 0.009$), media ($p = 0.0001$ and $p = 0.002$) and recanalized lumen ($p = 0.0001$ and $p = 0.001$). In CTOs >1 year old, the adventitia and IP NC numbers were similar and exceeded NC numbers found in the media ($p = 0.0001$) and recanalized lumen ($p = 0.0001$ and $p = 0.003$).**

Conclusions. **Angiographic CTO frequently corresponds to less than complete occlusion by histologic criteria. Age-related changes in IP composition from cholesterol laden to fibrocalcific may explain the adverse revascularization profile of older CTOs. IP NC growth derived from the adventitia increases with age and is strongly associated with IP cellular inflammation. IP NC formation may protect against the flow-limiting effects of IP growth.**

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Chronic total coronary occlusion (CTO) remains a major problem for percutaneous revascularization, with relatively low primary success rates and a high incidence of restenosis and reocclusion compared with those of subtotal stenoses (1–12). A long duration of occlusion and the presence of calcification are significant independent predictors of unsuccessful dilation (1,5,11). Both of these features are associated with increased difficulty in crossing total occlusions with a guide wire, which is the major limitation of percutaneous revascularization (13–15). The relation between the age of the total occlusion and the underlying histopathology remains unknown. Increasing fibrosis and calcification with advancing occlusion age may be the substrate for inability to cross CTOs with a guide wire. The presence of recanalized channels or loose fibrous tissue spanning the occluded segment of an apparent angiographic CTO may assist guide wire passage for percutaneous revascularization (16). This study describes the age-related histopathologic composition and neovascular channel (NC) patterns of CTOs. An improved understanding of the age-related change in intimal plaque (IP) composition and neovascular pattern of CTO may improve lesion selection for percutaneous revascularization.

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Abbreviations and Acronyms

bFGF = basic fibroblast growth factor
CTO = chronic total coronary artery occlusion
hpf = high power field
IP = intimal plaque
LAD = left anterior descending coronary artery
LCx = left circumflex coronary artery
NC = neovascular channel
PDGF = platelet-derived growth factor
RCA = right coronary artery
TIMI = Thrombolysis in Myocardial Infarction trial

Methods

Study cohort. The study cohort consisted of 96 angiographically documented CTO lesions from 61 patients undergoing autopsy over a 2-year period. Coronary angiography demonstrating interim development of a CTO in one or more coronary arteries was performed at our institution at least once in all patients and in the majority (95%) twice. The last coronary angiogram was performed within 3 months of death in all cases. Cases of acute plaque rupture with death resulting from thrombotic coronary occlusion were excluded. Total occlusion was defined in the present study as a lesion with abrupt vessel cutoff (100% angiographic diameter narrowing), and either Thrombolysis in Myocardial Infarction trial (TIMI) grade 0 or 1 anterograde flow distally (17).

Duration of occlusion. Lesion age was estimated either angiographically or clinically in one of two ways: 1) time from first observation of a subtotal lesion to CTO progression in the *same* coronary segment; 2) time from an index event (chosen in this study as myocardial infarction defined by clinical history, enzyme rise and Q waves in the electrocardiogram) to documentation of angiographic CTO, in the distribution appropriate for the prior myocardial infarction. This period was added to the time between the last angiographic study and autopsy to yield an estimate of lesion age. CTO age (estimated in weeks) was treated as a continuous variable for purposes of analysis. Ten CTO lesions were excluded from age-related morphologic analyses because lesion age could not be adequately assessed with these criteria. Arterial location, baseline patient demographic data and cardiovascular risk factors were all recorded at the time of angiographic CTO documentation.

Histopathology. Formalin-fixed autopsy hearts from 61 patients identified with angiographic CTO were serially sectioned at 2-mm intervals from the ostium to identify the zone of total occlusion. Coronary CTO segments were embedded in paraffin, and 5-μm sections were cut from segments representing the proximal, mid and distal parts of the CTO lesion. Sections were stained with hematoxylin-eosin, Lawson's elastic van Gieson, von Kossa (calcium) and Goldner's Masson trichrome (mineralization front) stains. Immunohistochemistry was performed for lymphocyte and macrophage antigens, von Willebrand factor (endothelial marker) and alpha-smooth muscle actin (vascular smooth muscle cell marker).

Histologic analysis. CTOs were categorized according to affected artery, and histologic variables were analyzed in each of four arterial zones: lumen, IP, media and adventitia. Percent lumen stenosis was derived from digital planimetry of lumen area, and internal elastic lamina area at the lesion site was calculated as (Internal elastic lumen area − Lumen area)/(Internal elastic lumen area) × 100. CTO histologic lumen stenosis was treated as a continuous variable for purposes of analysis. Within the recanalized lumen, presence or absence of old thrombus, iron and NC formation was recorded. Lumen recanalization score (0 to 4) was based on the number of NCs per high power field (hpf) (×150 magnification): 0/hpf, <5/hpf, 5 to 10/hpf, 11 to 15/hpf, >15/hpf.

Within the IP, an ordinal scale (0 to 6) was used to estimate the percent IP area occupied by the various plaque components (0%, <5%, 6% to 15%, 16% to 25%, 26% to 50%, 51% to 75%, >75%): collagen, calcium, elastin, cholesterol clefts, foam cells, giant cell atherophagocytes, mononuclear cells (lymphocytes, monocytes), and red blood cells (IP hemorrhage). The presence or absence of organized prior IP rupture was determined. IP composition was visually classified as "hard," "soft" or "mixed." Hard plaques were defined as predominantly fibrocalcific, with >50% IP area occupied by collagen and calcium. Soft plaques were defined as predominantly cholesterol laden, with >50% IP area occupied by cholesterol clefts, foam cells and loose fibrous tissue. Mixed plaques were those containing equal amounts of hard and soft components. Capillary neovascularization of the IP and media was scored ordinally (0 to 3) according to the number of NCs per hpf at ×150 magnification: 0/hpf, <5/hpf, 6 to 15/hpf, >15/hpf.

Aneurysmal dilation and atrophy of the media was graded as absent or present. Adventitial fibrosis was similarly evaluated. Cellular inflammation of the adventitia and media was graded according to percent of arterial circumference involved (0 to 4; 25% increments), density of inflammatory cells per hpf (0/hpf, <100/hpf, 100 to 150/hpf, 150 to 200/hpf, >200/hpf). Capillary neovascularization of the adventitia was scored (0 to 4) on the basis of number of NCs per hpf (0/hpf, <5/hpf, 5 to 10/hpf, 11 to 15/hpf, >15/hpf. All NCs were ordinally graded for size as small (150 to 250 μm) or large (>250 μm).

Statistical analysis. Descriptive statistics for all morphologic variables are expressed as mean value ± SEM, with median value and range quoted where appropriate. Ordinal morphologic data were compared with IP type by using contingency table analysis and Cochran-Mantel-Haenszel chi-square testing with Ridit scores. Associations between CTO age in weeks and ordinal morphologic data were tested by using Spearman's rank correlation. Continuous analysis of age and percent lumen stenosis–related data are displayed in the form of cumulative frequency distribution function curves. Ordinal logistic regression was utilized to compare inflammation and revascularization scores between differing vessel wall locations according to lesion age (<1-year and >1-year categories).

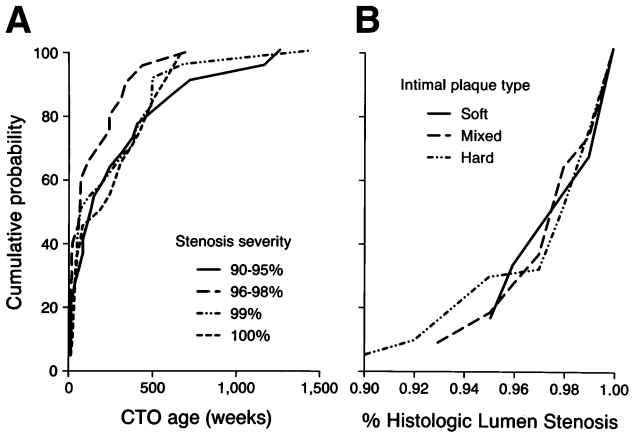


Figure 1. A, Cumulative frequency distribution function curves for differing chronic total occlusion (CTO) lumen stenosis categories displayed as a continuous function of CTO age. No significant effect of CTO age on percent lumen stenosis is evident. **B,** Cumulative frequency distribution function curves for differing intimal plaque (IP) types as a continuous function of percent histologic lumen stenosis. No significant interrelation between percent lumen stenosis and IP type is evident.

Results

Three lesions with histologic lumen stenoses <90% were excluded from analysis, as these were clearly subtotal occlusions at autopsy. Ten lesions could not be accurately dated and these were excluded from analysis based on CTO age. Finally, 96 lesions from 61 autopsy patients were available for analysis. Of all angiographic CTOs, 43% were in the right coronary artery (RCA) distribution with 30% and 27% in the left anterior descending (LAD) and the left circumflex coronary artery (LCx), respectively. A total of 64% of all CTOs were >1 year old, 19% <3 months old, 17% 3 months to 1 year old, 29% 1 to 5 years old and 35% >5 years old. Sixty-four percent of CTOs contained predominantly fibrocalcific IP, 11% contained predominantly cholesterol-laden IP and 25% were of mixed IP type. Mean patient age at the time of angiographic CTO documentation was 63.4 ± 1.3 years (range 40 to 88). Mean cholesterol level was 285.5 ± 8.0 mg/dl (range 226 to 378) and mean triglyceride level was 244.3 ± 43.1 mg/dl (range 99 to 965). Insulin-dependent diabetes mellitus was more frequently observed (36% vs. 11%, $p = 0.03$) in patients with CTO <1 year old than in those with CTO >1 year old. It was also more frequent in patients with predominantly cholesterol-laden or mixed CTO than in those with fibrocalcific CTO (36% vs. 11%, $p = 0.02$). No significant differences in CTO age or IP composition were observed for other cardiovascular risk factors.

The majority (78%) of angiographic CTOs were ≤99% occluded by histopathologic assessment (25% were 90% to 95% occluded, 24% were 96% to 98% occluded, 29% were 99% occluded, and 22% were 100% occluded). No relation was observed between percent lumen stenosis and either CTO age (Fig. 1A) or IP type (Fig. 1B). Cumulative frequency distribution curves for differing percent lumen stenosis categories as a continuous function of age are illustrated in Figure 1A. Similar cumulative frequency distribution curves for different IP type categories as a continuous function of histologic lumen stenosis are illustrated in Figure 1B. Functional total occlusions (angiographic CTO with <100% histologic lumen stenosis) predominated at all occlusion ages.

CTO age analysis. *Lumen.* No significant differences were observed in the frequency of organized lumen thrombus with change in CTO age. Lumen recanalization was extensive (Fig. 2, A and B) and frequent (59% of all CTOs). The frequency of lumen recanalization channels were similar across all CTO ages. The frequency of large (59% of all CTOs) and small (41% of all CTOs) lumen recanalization channels was also similar across all CTO ages. Communication between lumen recanalization channels and the IP neovasculature was rarely observed.

IP. No significant difference in the frequency of organized platelet/fibrin thrombus over previously denuded small areas of IP was noted with respect to CTO age or IP type. Evidence of IP focal iron and hemosiderin deposition was observed at sites of previous IP hemorrhage. The frequency of IP focal iron and hemosiderin deposition was similar at all CTO ages. Extensive recanalization of the IP was frequently evident (Fig. 2C). IP NCs were observed in 85% of CTOs >1 year old as compared with 74% of CTOs <1 year old. This increase in numbers of IP NCs with CTO age did not reach statistical significance ($p = 0.06$). In almost all CTO lesions, IP NCs were observed to directly communicate with the adventitial vasa vasorum. In a few lesions, communication between lumen recanalization channels and IP capillaries was also observed. There was no significant variation in the frequency of small or large IP NCs among all four CTO age groups.

A significant increase in the frequency of predominantly fibrocalcific IP lesions was evident with increasing CTO age, whereas cholesterol-laden or mixed IP lesions predominated as CTO age decreased (Fig. 3A, $p = 0.003$). Thus, the frequency of cholesterol-laden ($p = 0.0007$) and foam cell–rich IP ($p = 0.0007$) declined with advancing CTO age (Fig. 3B and 4). In contrast, the frequency of IP calcification increased with advancing CTO age ($p = 0.008$) (Fig. 4 and 5).

The frequency of IP giant cells decreased with advancing CTO age ($p = 0.01$). Cellular inflammation of the IP was frequently observed (78% of all CTOs). No significant difference was observed in the frequency or severity of IP inflammation by lymphocytes and monocyte-macrophage cells among CTOs of all ages. IP NCs were most frequently observed within and adjacent to IP sites infiltrated by lymphocytes and monocyte-macrophages. Both the number of IP NCs ($p = 0.0001$) and the size of IP NCs ($p = 0.0001$) increased with progressive cellular inflammation of the IP.

Media. Figure 6 illustrates the various NC patterns observed, including lumen recanalization (Fig. 6A), IP channels (Fig. 6B) and adventitial/medial neovascularization (Fig. 6, C and D). Well developed small to large NCs were observed traversing the media from the adventitia in CTOs of all ages (Fig. 6D). The number ($p = 0.04$) and size ($p = 0.02$) of these

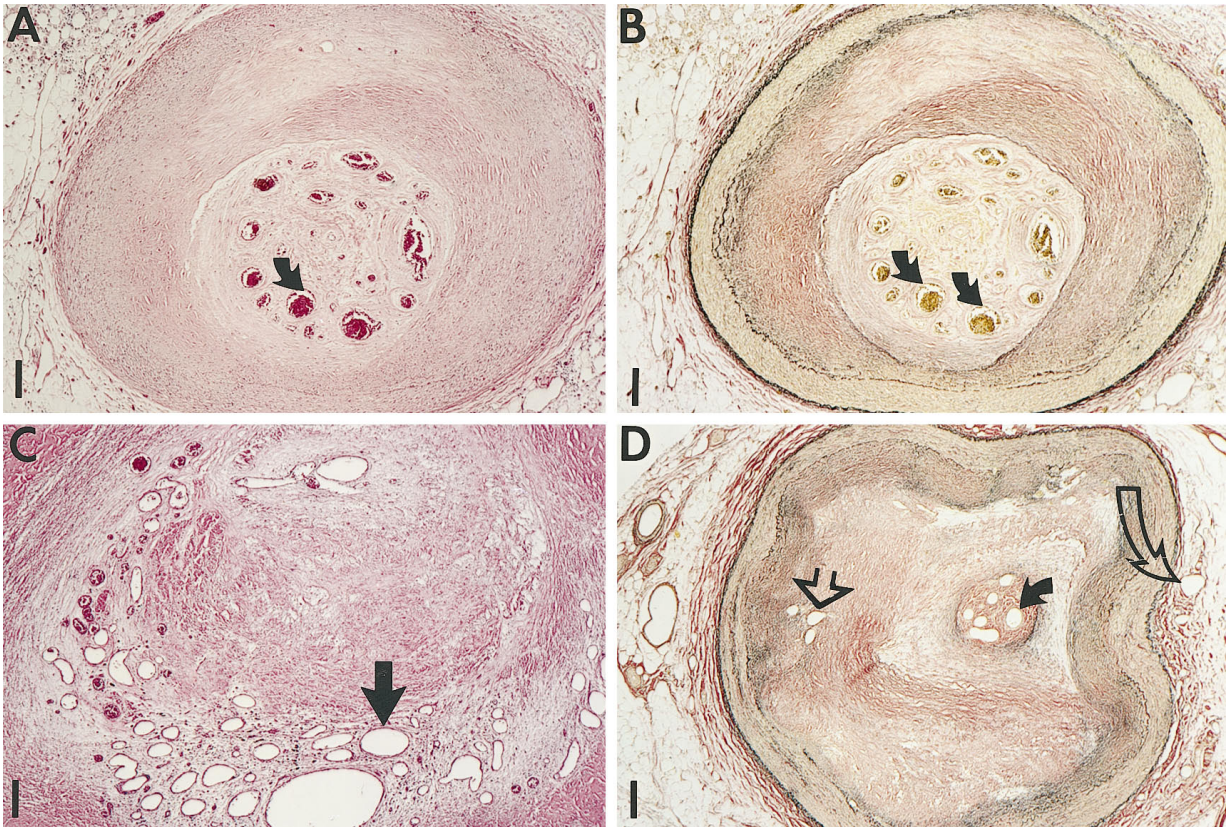
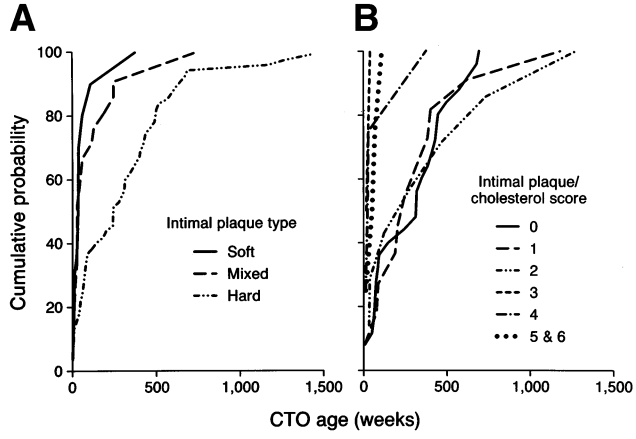


Figure 2. A and **B,** Low power views (hematoxylin-eosin and Lawson's elastic van Gieson stains) of chronic total occlusion lumen recanalization by large central neovascular channels (NCs) (**arrows**). **Scale bar** indicates 385 μm. **C,** High power view (hematoxylin-eosin stain) demonstrating extensive small, medium and large intimal plaque (IP) NCs (**arrows**). **Scale bar** indicates 167 μm. **D,** Low power view (elastic van Gieson stain) demonstrating central lumen, IP and adventitial NC formation (**solid, open** and **curved open arrows,** respectively). **Scale bar** indicates 500 μm.

medial NCs increased with progressive cellular inflammation of the IP. The number and size of medial NCs and cellular inflammation did not vary with CTO age. There was no association of aneurysmal dilation of the media, medial atrophy and medial cellular inflammation with CTO age. A dense inflammatory infiltrate of lymphocytes and monocyte-macrophages was frequently observed within the media, and within both IP and adventitia immediately adjacent to the media, in CTOs of all ages (Fig. 7).

Adventitia. The adventitia was extensively revascularized in CTOs of all ages with both small and large NCs (Fig. 6, C and D). The frequency of adventitial fibrosis, number of adventitial NCs and the distribution of adventitial NC size was similar across all CTO ages. In CTOs <1 year old, the adventitia was associated with a greater number of NCs relative to IP ($p = 0.006$), media ($p = 0.001$) and lumen ($p = 0.001$) locations (Fig. 8A). In CTOs >1 year old (Fig. 8B), the adventitia was associated with a similar number of NCs relative to the IP, but it continued to be associated with higher NC numbers relative to medial ($p = 0.001$) and lumen ($p = 0.001$) locations (Fig. 8B). The overall magnitude for NC numbers was adventitia > IP ≥ media ≥ lumen for CTOs <1 year old and adventitia ≥ IP > media ≥ lumen for CTOs >1 year old. In CTOs <1 year old, adventitial NC size was larger than that found in the IP

Figure 3. A, Cumulative frequency distribution curves for differing intimal plaque (IP) types as a continuous function of chronic total occlusion (CTO) age. Soft or lipid-laden CTO lesions predominate at younger CTO ages; hard fibrocalcific lesions increase in frequency with CTO age ($p = 0.0003$). **B,** Cumulative frequency distribution function curves for differing CTO IP cholesterol categories as a continuous function of CTO age. IP cholesterol content is observed to increase with declining CTO age ($p = 0.0007$).



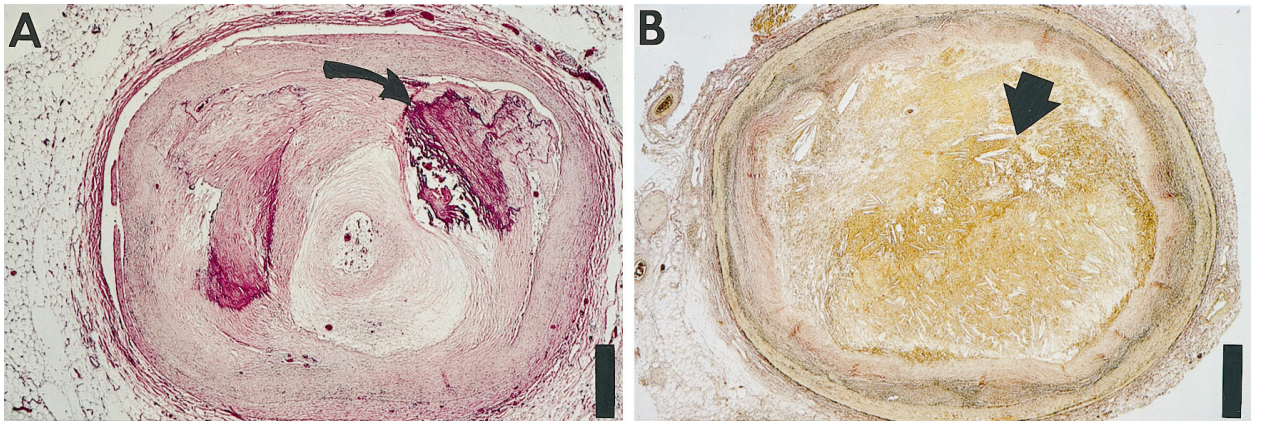


Figure 4. A, Low power view (hematoxylin-eosin stain) of a representative hard or fibrocalcific chronic total occlusion (CTO) with extensive calcification **(arrows)**. **B,** Low power view (elastic van Gieson stain) of a representative soft or lipid-laden CTO intimal plaque with extensive cholesterol deposition **(arrow)**. **Scale bar** indicates 1,266 μm.

(p = 0.009), media (p = 0.009) and recanalized lumen (p = 0.001). In CTOs >1 year old, adventitial and IP NC sizes were similar and exceeded NC sizes found in the media (p = 0.0001) and recanalized lumen (p = 0.0003).

Adventitial cellular inflammation (lymphocytes, monocytes, macrophages) was more frequent (p = 0.01), more extensive (p = 0.01) and more intense (p = 0.01) in younger than in older CTOs. Cellular inflammation of the adventitia was less than in the IP (p = 0.009) but greater than in the media (p = 0.03) in CTOs <1 year old (IP > adventitia > media, Fig. 8C). In CTOs >1 year old, cellular inflammation of the IP still exceeded that found in the adventitia (p = 0.0001), with adventitial inflammation similar to that found in the media (IP > adventitia ≥ media, Fig. 8D). In all cases, as with the IP, a close anatomic relation was observed between adventitial NC formation and adventitial cellular inflammation.

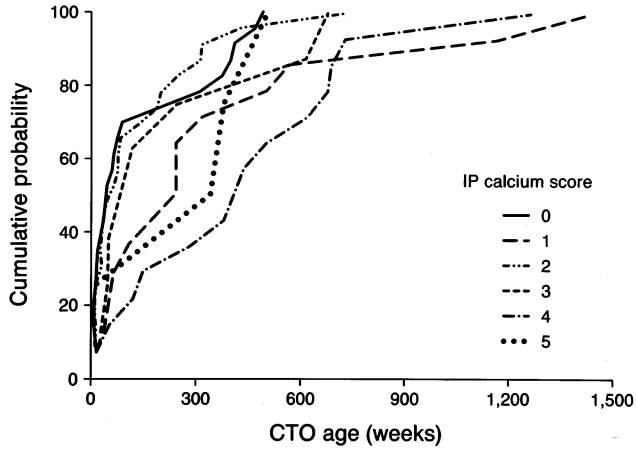
Intimal plaque composition analysis. No relation was observed between histologic percent lumen stenosis and IP composition of CTO (Fig. 1B). All CTOs visually classified as predominantly cholesterol laden (soft) contained ≤25% IP collagen, ≤15% calcium and ≤15% elastin. Of all lipid-laden CTOs, 82% contained >50% cholesterol and 89% contained >5% foam cells within the IP. All CTOs visually classified as hard contained <25% cholesterol, and 72% showed no evidence of any cholesterol deposition within the IP. Of all fibrocalcific CTOs, 59% contained >50% collagen, 28% contained >25% calcium and 10% contained >25% elastin. There was a significant increase of the predominance of soft or cholesterol-laden lesions at young CTO ages and hard fibrocalcific lesions at older CTO ages (p = 0.0003, Fig. 3A). IP giant cell atherophagocytes were all significantly more frequent (p = 0.001) in soft (55%) or mixed (42%) lesions than in hard CTOs (12%). The frequency of lumen recanalization channels was similar across all IP types. No difference was observed in the number or size of NCs in lumen, IP, media or adventitial locations among CTOs of hard, soft or mixed IP composition. Adventitial neovascularization was similarly extensive in all three CTO types. The frequency of medial atrophy or aneurysmal dilation and IP cellular inflammation was similar across all IP types. Medial cellular inflammation was more frequently observed in soft (18%) or mixed (17%) CTOs than in hard (5%) lesions (p = 0.05).

Arterial location analysis. Medial NCs in CTOs of the RCA were more numerous (p = 0.05) and larger (p = 0.04) than those in CTOs located in either the LAD or the LCx. Medium and large medial NCs were present in 80% of RCA, 65% of LCx and 55% of LAD occlusions. The presence of IP inflammation (88% RCA, 69% LCx, 73% LAD) was greater in RCA occlusions than in LCx or LAD occlusions (p = 0.06).

Discussion

In the present study, no relation was evident between histologic lumen stenosis and either lesion age or IP composition. Of all angiographic CTOs, 49% exhibited residual <99%

Figure 5. Cumulative frequency distribution curves for chronic total occlusion (CTO) intimal plaque (IP) calcium categories as a continuous function of CTO age. IP calcium content is observed to increase with advancing CTO age (p = 0.008).



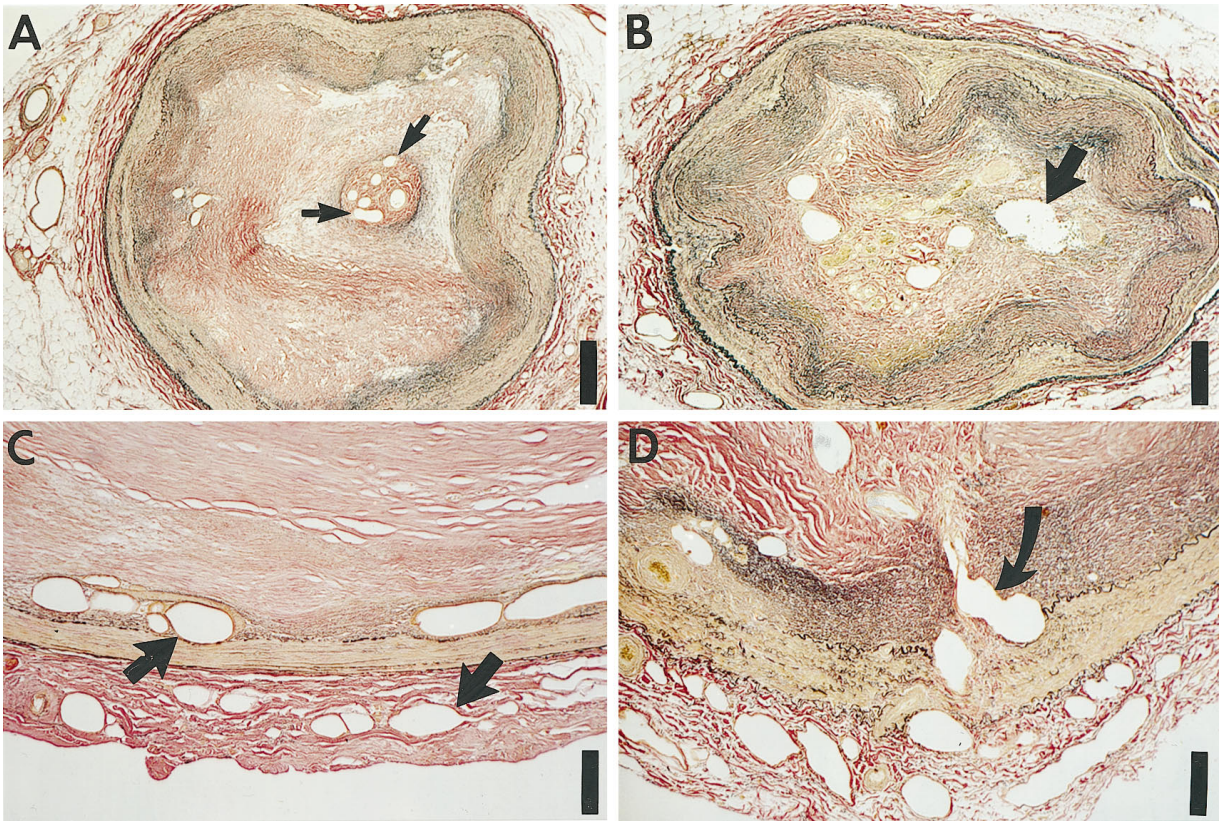


Figure 6. A, Low power view (elastic van Gieson stain) of an advanced chronic total occlusion (CTO) lesion demonstrating lumen recanalization with small and medium neovascular channels (NCs) (**arrows**). **Scale bar** indicates 800 μm. **B,** Low power view (elastic van Gieson stain) of a CTO, demonstrating several large intimal plaque (IP) NCs (**arrows**) within the IP. **Scale bar** indicates 534 μm. **C** and **D,** High power views (elastic van Gieson stain) demonstrating several large NCs within the adventitia and also traversing the media between the adventitia and the IP (**curved arrow**). **Scale bar** indicates 320 μm.

lumen stenosis by histologic criteria despite angiographically documented total occlusion with distal TIMI grade 0 or 1 anterograde flow. A variety of mechanisms may underlie this observation, including vasospasm, the presence of a functional coronary occlusion due to a high distal coronary pressure exerted by competitive retrograde collateral flow, or the recanalization of prexistent lumen thrombus (18,19). Previous series (6) have emphasized the lower primary success rates (53% to 81%) and higher recurrence rates (50% to 60%) for CTOs than for subtotal stenoses (>90% initial success rate). Functional occlusions also have a higher primary success rate and a lower reocclusion rate than do complete anatomic occlusions (11,20). A greater predominance of functional occlusions was observed in younger CTO lesions in the present study.

Revascularization of total occlusions. Percutaneous revascularization of CTOs has steadily increased to ~10% to ~20% of all coronary angioplasty procedures in large centers (6). The major cause of revascularization failure remains the inability to cross the CTO with a guide wire. Both a short duration of occlusion and the absence of lesion calcification have been previously identified (1,5,14,21,22) as predictors of revascularization success. The present study suggests a histologic basis for these observations, as younger CTO lesions are observed to be predominantly soft or lipid laden whereas older lesions are typically hard or fibrocalcific and therefore less favorable to guide wire passage or dilation. The current study documents the frequent occurrence of IP calcification, even in CTOs <3 months old (54%), and an increase in both the frequency and the severity of IP calcification with advancing lesion age. This age-related increase in the calcium and collagen content of CTOs may in part underlie the progressive difficulty in crossing occlusions of advanced duration.

Neovascularization of CTOs. A striking feature of all CTO angioplasty series is the paucity of complications related to occlusion site, such as death, infarction or need for emergency bypass surgery (8,9). This finding has been attributed to the protection afforded by well developed collateral flow. The present histologic study confirms the extensive neovascularization of all vessel wall locations, irrespective of lesion age or lumen stenosis severity (Fig. 2, 6 and 8). Increased numbers of IP capillaries are observed with increasing occlusion age (Fig. 8). In CTOs <1 year old, the adventitia is the predominant vessel wall location of NC formation in terms of both number and size. In CTOs >1 year old, IP capillary numbers and size increase and are not significantly different from adventitia. Both IP and adventitial NC numbers remain greater relative to the lumen or media across all CTO age groups. The high

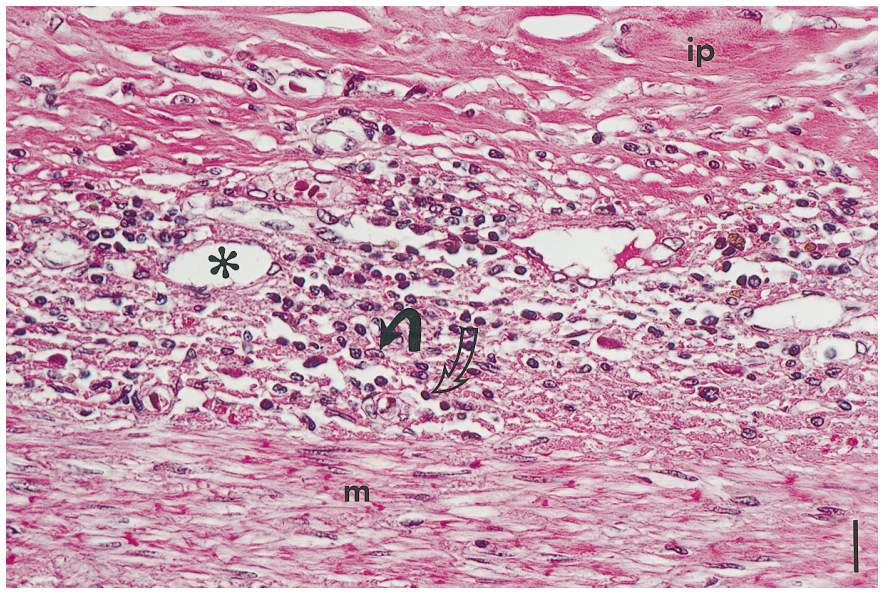


Figure 7. High power view (hematoxylin-eosin stain) of dense cellular inflammation consisting of lymphocytes **(open arrow)** and macrophages **(closed arrow)** within the intimal plaque (ip) and media (m) of a chronic total occlusion immediately adjacent to intimal plaque neovascular channels **(asterisk)**. **Scale bar** indicates 100 μm.

frequency (47% to 67%) of large (>250 μm) NCs in all vessel wall locations even in CTOs <1 year old suggests that the enlargement of growing NCs within CTO is an early event. The age-related increase in CTO neovascularization may therefore result largely from an increase in number of NCs, as well as an increase in channel size.

Comparative studies of neovascularization. The large numbers of adventitial NCs observed across a wide spectrum of CTO age and lumen stenosis severity argues for a readily recruitable neovascular system even in younger lesions. In the present study, NCs were found traversing directly from the adventitial vasa vasorum across the media into the IP (Fig. 6D). The observed increase in IP neovasculature in CTO lesions >1 year old is therefore consistent with the active ingrowth of NCs from the adventitial vasa vasorum. Microsphere studies (23) indicate that the increased blood flow through the vasa vasorum of the intima-media observed in atherosclerosis, occurs primarily by proliferation of new microvessels (23). A recent postmortem study of subtotal atherosclerotic lesions (24) has shown that in lesions with >70% lumen stenosis, newly formed intimal vessels originate mainly from the adventitial vasa vasorum and only rarely from the coronary lumen. Regional hypoxia in the deeper zones of the media is postulated to promote the process of neovascular growth from adventitial blood vessels (25,26). In contrast, the development of lumen recanalization channels and their extension into the intima may result from thrombus-derived angiogenic stimuli (26). Perfusion studies utilizing india ink

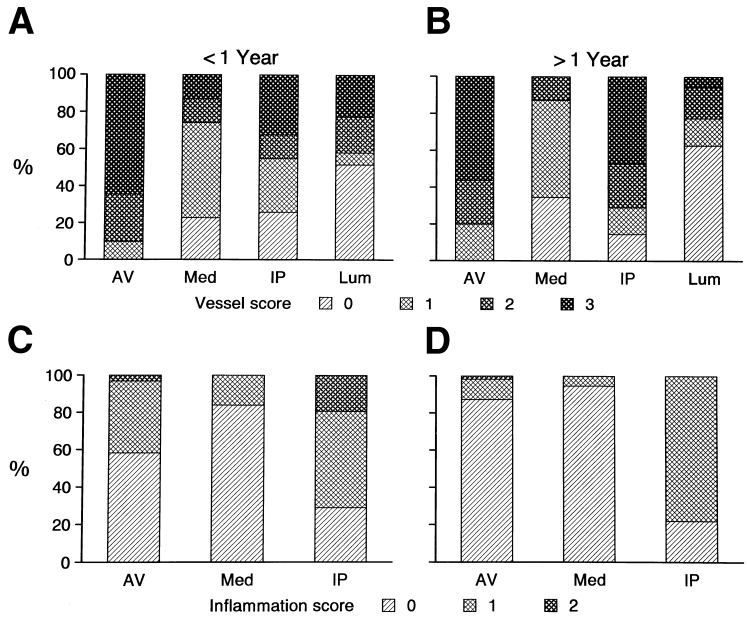


Figure 8. Frequency distribution plots. **A,** Neovascular channel (NC) number score according to vessel wall location in chronic total occlusions (CTOs) <1 year old. The adventitia (AV) is associated with a greater number of NCs relative to the intimal plaque (IP) ($p = 0.0006$), media (Med) ($p = 0.0001$) and recanalized lumen (Lum) ($p = 0.0001$). **B,** NC number score according to vessel wall location in CTOs >1 year old. The number of NCs in the adventitia is similar to that in the IP but exceeds that found in either the media ($p = 0.0001$) or recanalized lumen ($p = 0.0001$). **C,** Cellular inflammation score according to vessel wall location in CTOs <1 year old. The IP is associated with a greater intensity of cellular inflammation relative to that in either the adventitia ($p = 0.009$) or the media ($p = 0.0001$). **D,** Cellular inflammation scores according to vessel wall location in CTOs >1 year old. The IP has a greater intensity of inflammation than that of the adventitia ($p = 0.0001$), which is similar to that of the media.

and silicone polymer have demonstrated increased vasa vasorum in regions of coronary atherosclerosis, both as bridging NCs and as a dense meshlike capillary plexus extending from the adventitia across the media into the intima (27–29).

Adventitia. Observations from the present study indicate that large NCs (>250 μm) were frequently present within the adventitia of CTOs of all ages. The number of adventitial NCs exceeded those found in all other vessel wall locations in CTOs <1 year old, and these were accompanied by an equivalent number of IP NCs in CTOs >1 year old that were connected with and presumably derived from the adventitial vasa vasora. Because coronary collateral channels <200 μm in diameter are not visualized by angiography (30), two conclusions may be drawn from these pathologic observations. 1) Angiographic bridging collateral vessels across CTOs most likely represent enlarged NCs arising from proliferated vasa vasorum within the adventitia (27). 2) Angiographic assessment of the anterograde collateral system of CTOs is a poor indicator of the true microvascular collateral supply observed histologically in these lesions. This disparity in angiographic and histologic collateral appearance may arise from vessel spasm, inadequate contrast filling of NCs <200 μm, as well as high distal coronary pressure that limits anterograde flow within these collateral vessels (18,31).

The presence of angiographic bridging collateral vessels spanning the occluded segment has been identified as a major predictor of procedural failure (5,12,15,32–34). Bridging collateral channels are thought (27) to represent NCs arising from enlarged vasa vasorum. When compared with 324 CTOs without such collateral channels, similar primary success rates were obtained for both groups, but lesions with bridging collateral channels were found to have been present for a longer time (35). This finding suggests that angiographic bridging collateral vessels are typically associated with older coronary occlusions that may be intrinsically more difficult to cross and dilate. A prior histologic study (16) of 10 CTOs demonstrated the presence of small lumen recanalization areas traversing CTOs with tapering morphology or short occluded segments. These channels or the loose connective tissue surrounding them may provide a route for successful guide wire passage (36). The present study of 96 CTOs confirms these findings by demonstrating that some degree of histologic lumen patency is present in the majority of apparent angiographic CTO.

Cellular inflammation and neovascularization. Prominent cellular inflammation of CTOs by lymphocytes, monocytes and macrophages was frequently observed in this study within the intima, media and adventitia. Frequent colocalization and predominance of cellular inflammation and neovascularization within the IP and adventitia of all CTOs suggest that these processes may be closely related. This view is also borne out by the observed association between increasing IP and media neovascularization and progressive IP cellular inflammation. Whether this cellular inflammation represents the cause or effect of neovascularization is unclear. Lymphocytes and monocyte-macrophages may play an active role in both angiogenesis and atherosclerotic lesion progression (24,37) by producing a variety of mitogenic and angiogenic factors including basic fibroblast growth factor (bFGF), heparin-binding epidermal growth factor–like factor, platelet-derived growth factor (PDGF), tumor necrosis factor alpha and transforming growth factor beta (38,39). In atherosclerotic plaques, expression of the bFGF receptor (FGFR-1) is largely confined to the adventitial microvasculature, suggesting a direct role for T lymphocytes and macrophage-derived bFGF in adventitial neovascular growth (40). Stimulation of smooth muscle cell migration and proliferation by macrophage and T lymphocyte–derived PDGF and bFGF may also contribute to atherosclerotic progression (41).

The increased size and number of medial NCs observed in CTOs of the RCA as compared with the LCx or LAD has previously been described only in pigs (42). The greater propensity for RCA occlusion neovascularization may relate to the lower transmural pressure gradient experienced by NCs within the right ventricular wall as compared with the left ventricle.

Limitations of the study. The present retrospective study did not include the performance of postmortem coronary angiography. Thus, we cannot exclude the occurrence of spontaneous thrombus recanalization as a mechanism for the occurrence of histologic lumen patency at sites of previously documented angiographic total occlusion. The dating of the duration of occlusion in this study remains an estimate. However, all autopsies were performed within ≤3 months of the last antemortem angiogram, and the high frequency (85%) of angiographically documented progression from subtotal to total occlusion has ensured the best clinical approximation possible.

Conclusions. Angiographic appearance of CTO frequently corresponds with residual lumen patency by histologic criteria. Marked age-related histologic changes occur in both IP composition and neovascular patterns of CTO. The age-related change in IP composition from predominantly lipid laden to fibrocalcific may serve to explain the lower primary success and higher long-term recurrence rates observed for percutaneous revascularization of CTOs as compared with subtotal stenoses. The adventitia and IP of total occlusions are the predominant zones of cellular inflammation and neovascularization within the arterial wall of all CTOs. In CTOs of all ages, a close relation in terms of both location and intensity is observed between cellular inflammation (T lymphocytes and monocyte-macrophages) and vessel wall neovascularization. Most IP neovasculature arises directly from adventitial vasa vasorum and only rarely directly from the lumen or from lumen recanalization channels. The observed increase in CTO neovascularization with age relates more to an increase in numbers of NCs than to an increase in NC size. Extensive development of vessel wall NCs, particularly within the adventitia and IP, may serve to protect against the flow-limiting effects of IP growth and progressive lumen stenosis leading to CTO. Availability of a patent residual lumen (or recanalization channel)

and age-related changes in IP composition may be key determinants of successful guide wire passage and dilation of CTO.

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